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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,472	03/29/2002	Eric Lam	RU-0170	3041

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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/009,472	LAM ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the c ver sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-9 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 10-6-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the previous rejection under 35 U.S.C. 112, 1st paragraph (written description) in view of claim amendments and persuasive arguments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-5 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Nucleic Acids Res., Apr 15 1998, Vol. 26(8):2034-2035), Mattioni et al. (Methods in Cell Biol., Vol. 43:335-352, 1994) and Hull et al. (Methods in Mol. Biol., 1995, Vol. 49:125-141). Claims 1, 4-5 and 9 are specifically drawn to a fusion protein comprising a ß-glucuronidase and a hormone binding domain (HBD) linked through a predetermined protease cleavage site or sequence, wherein the ß-glucuronidase remains inactive as long as it is fused to HBD but is rendered active upon cleavage by said protease such that it is free from HBD.

Xu et al. teach in general the use of chimeric proteins comprising a repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter

domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site. The reference discloses a chimeric protein comprising the green fluorescent protein (GFP) and the blue fluorescent protein (BFP) linked together through a linker comprising a spacer and a caspase cleavage sequence. The two fluorescent proteins both act as reporters and repressors of each other. The placement of the two fluorescent proteins in close proximity reduces the fluorescence intensity compared to the intensity of the individual proteins. The cleavage by the predetermined protease such as a caspase eliminates the reduction in fluorescence. However, the reference does not teach the use of a reporter enzyme such as ß-glucuronidase and its repressor for identifying the protease of interest.

Hull et al. provide extensive information regarding the use of ß-glucuronidase as a reporter enzyme and method to use the same in reporter assays for reporting a variety of activities. From this reference it is clear to those skilled in the art that the use of ß-glucuronidase in reporter systems was well known in the art and that said enzyme was most favored for developing a reporter system.

Mattioni et al. teach regulation of protein activities by fusion to steroid binding domains. The reference teaches that an alternate method to inducible expression of a protein activity can be developed by making fusion protein, comprising the protein of interest whose activity needs to be controlled (i.e., reporter domain), and a HBD sequence linked at the N-terminal or C-terminal of the reporter protein. The reference teaches that natural ligands of the HBDs in the

cell bind to the HBDs and create a stearic hindrance which renders the reporter inactive. The reference also teaches that the common HBD used is that of the example of Glucocorticoid receptor (GR), which is ubiquitously expressed in mammalian cells. The reference teaches that HSP90 binds to the GR-HBD and creates a stearic hindrance which renders any protein fused to it inactive. The reference teaches that the reporter can be activated by adding alternative ligands for the HBDs or by cleaving away the stearic hindrance which will not inactivate the reporter protein and thereby the reporter activity can be modulated. However, this reference does not teach the use of a protease cleavage site between the HBD and reporter and the use of a protease in order to activate the reporter.

With the above references in hand it would have been obvious to one of ordinary skill in the art to combine the teachings and arrive at the instant invention. Based on the method of Xu et al. it would have been obvious to those skilled in the art to develop a fusion protein comprising a repressor domain which represses the activity of the fused polypeptide through a protease cleavage site such that upon cleavage by the protease of interest, the fused polypeptide would be rendered active and whose activity can be monitored. With such an idea in hand, it would have been obvious to those skilled in art to look for the most commonly used reporter enzyme and its repressor. Such information is provided by the combined teachings of Hull et al. which teaches the extensive use of ß-glucuronidase its use as a reporter and ways and means to monitor its activity and Mattioni et al. which provides the information regarding the use of enzyme repressors and their use in controlling enzyme activity.

With all the above teachings in hand it would have been obvious to those skilled in the art to replace the repressor and the reporter taught by Xu et al. with ß-glucuronidase and its

repressor and construct a fusion protein comprising a reporter such as ß-glucuronidase and the HBD such as the GR-HBD linked through a predetermined protease cleavage site such as that of a specific caspase and use it to determine the presence of said protease. One of ordinary skill in the art would have been motivated to do so in order to develop an alternate system to that developed by Xu et al. i.e., an enzyme based fusion protein and assay as opposed to the fluorescent protein based fusion protein and assay developed by Xu et al. One of ordinary skill in the art would have a reasonable expectation of success since all the above references teach all the important aspects of the invention.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that for an obvious rejection, the claimed invention must be considered as a whole and the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination and the references must be viewed without the benefit of hindsight vision afforded by the claimed invention and that there must be a reasonable expectation of success. Examiner reiterates that he has in fact analyzed the claims and then rejected them based on all the above. The invention when considered as a whole very closely resembles the invention of Xu et al. i.e., a fusion polypeptide comprising two peptides linked through a peptide cleavage site such that when cleaved by a specific protease that cleaves at the cleavage site, the two peptides are liberated which can be identified by different means and be concluded that the protease enzyme being assayed is that which has its cleavage sequence the same as that in the fusion polypeptide. As explained in the rejection, the only difference from

Xu et al. and the instant invention is that the peptides have different properties and therefore the means of detecting the liberated peptide is different. Therefore contrary to applicant's argument the method taught by Xu et al. does not operate in the exact opposite manner of the Xu et al. Furthermore, it should also be noted that when the invention is considered as a whole, the overall principle in the instant invention is identical with that of Xu et al., i.e., the properties of the two individual peptides are changed or regressed or inactivated as long as they are linked together and they demonstrate their specific characteristic only after being separated due to the cleavage. Therefore, on this count as well, contrary to applicant's argument the Xu et al. reference does not teach away from the invention.

Next applicants argue that only a hindsight vision afforded by the claimed invention would motivate the skilled practitioner to combine the references as argued by the Examiner. Examiner respectfully disagrees with such an argument. Here again contrary to applicant's argument, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Examiner has based the rejection only taking the knowledge which was within the level of ordinary skill at the time of invention. The use of fusion polypeptides comprising a specific protease cleavage site and whose individual (i.e., the polypeptides in the fusion protein) property/function was inhibited as long as they were fused was well known, as was the knowledge to detect the activity/property/function of the individual polypeptides after

being cleaved by the specific protease. Irrespective of the properties of the polypeptides, the above type of specific assay for identifying a specific protease activity was well known in the art. The use of enzymes and the hormone binding peptides to temporarily inactivate the enzyme in the form of fused protein was also well known as taught by Hull et al. Based on this type of knowledge that was well known in the art the question of hindsight reconstruction does not arise at all. All that the applicants have done is developed an alternate type of fusion protein to the one that is already well known in the art, for example the fluorescence based fusion protein of Xu et al. In the above rejection, Examiner has argued just that as the motivation which comes from the art and is not suggested by the cited references. In view of all the above Examiner continues to maintain the above rejection.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Nucleic Acids Res., Apr 15 1998, Vol. 26(8):2034-2035), Mattioni et al. (Methods in Cell Biol., Vol. 43:335-352, 1994) and Hull et al. (Methods in Mol. Biol., 1995, Vol. 49:125-141) as applied to claims 1-2, 4-5, 9, and further in view of the common knowledge in the art. Claim 6-8 in this instant application are drawn to chimeric proteins for detecting the presence of predetermined protease, comprising a plurality of reporter or repressor domains or cleavage sites, wherein the repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain

comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site.

The reference of Xu et al., Mattioni et al. and Hull et al. as it applies to chimeric proteins comprising single reporter and repressor and cleavage sites have been discussed above. Using the teachings of the above references it would have been obvious to those skilled in the art to have multiple domains such that the signal intensity obtained for the reporter domain, whether it is fluorescence as in Xu et al. reference or the activity of the reporter enzyme as in the instant case would be more intense and its detection be easier. Because of the simplicity and ease of use of the technique it would have also been obvious to one of ordinary skill in the art to use multiple protease cleavage sites and detect the presence of multiple set of proteases. One of ordinary skill in the art would have been motivated to do so in order to develop intense signal during the assay.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the above rejection, applicants have traversed the rejection and argue that this rejection must be withdrawn for the same set of reasons mentioned in the argument for the previous obviousness rejection. Examiner respectfully disagrees with the applicants that such an argument is persuasive to overcome the above rejection for reasons set forth in the previous argument (above) and continues to maintain the above rejection.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

January 10, 2005